Treatment of the Dumping Syndrome with the Somatostatin Analogue SMS 201-995

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In six patients suffering from severe early dumping and six patients with late dumping after peptic ulcer surgery, the effect of the somatostatin analogue SMS 201-995 was compared with placebo. In early dumpers subcutaneous administration of 50 μg SMS 201-995 prior to meal ingestion induced a strong improvement of dumping symptoms as reflected by a decrease of the Sigstad dumping score from 12 ± 2 during placebo to 5 ± 2 ($p < 0.05$). Furthermore, the postprandial increase of pulse rate was abolished; maximum pulse rate decreased from 85 ± 7 beats/min to 67 ± 7 beats/min ($p < 0.05$). SMS 201-995 did not significantly affect postprandial changes in packed cell volume. In late dumpers 50 μg SMS 201-995 reduced peak plasma insulin after oral glucose from 173 ± 16 mU/L during placebo to 35 ± 9 mU/L during SMS 201-995 ($p < 0.05$) and increased individual plasma glucose nadirs from 1.9 ± 0.3 mmol/L to 7.5 ± 3.3 mmol/L ($p < 0.01$). Both in early and late dumpers SMS 201-995 improved postprandial expiratory breath hydrogen excretion indicating slowing of gastrointestinal hurry. SMS 201-995 is a powerful therapeutic agent for the management of patients suffering from the dumping syndrome after gastric surgery.

THE DUMPING SYNDROME can be a serious and disabling complication after gastric surgery.[1–3] The syndrome is precipitated especially by heavy or carbohydrate-rich meals (1–3). Symptoms of early dumping occur during or immediately after meal ingestion and consist of both gastrointestinal and cardiovascular components including nausea, epigastric distress, meteorismus, borborygmia, palpitation, weakness, exhaustion, dyspnea, dizziness, and syncope.[2] The symptoms of late dumping including a feeling of warmth, sweating, shakiness, dizziness and difficulty in concentration occur 1 to 3 hours later and are attributed to reactive postprandial hypoglycemia.[3] Rapid gastric emptying of hyperosmolar food resulting in a shift of water and elektrolytes to the small intestinal lumen with subsequent hemoconcentration and abnormal gut endocrine responses are generally thought to play a crucial role in the pathogenesis of the syndrome.[1–7] So far, methods of treatment including dietary fibers and α-glucosidase inhibitors have met with only limited success.[8–11] Recently, it has been suggested that somatostatin and possibly its analogues might be of value in the management of circulatory and metabolic disturbances associated with the syndrome.[12] The present study was therefore undertaken to determine the effect of SMS 201-995, a long-acting analogue of somatostatin, on clinical symptoms, pulse rate, packed cell volume, plasma insulin, plasma glucose, and breath hydrogen excretion in patients suffering from postprandial dumping.

Patients and Methods

Six patients (three men, three women; 33–48 years) with early dumping selected on the basis of the clinical diagnostic index divised by Sigstad[13] participated in the study. All patients had undergone a partial gastric resection for peptic ulcer disease at least 1 year before. In addition, six patients (three men, three women; 26–48 years; one highly selective vagotomy, five partial gastrectomy) with late dumping were studied. These patients were selected on the basis of having a history suggestive of postprandial hypoglycemia, a plasma glucose of less than 3.0 mmol/L at least 60 minutes after ingestion of 50 g glucose/m^2 body surface, and hypoglycemic

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Submitted for publication: August 13, 1987.

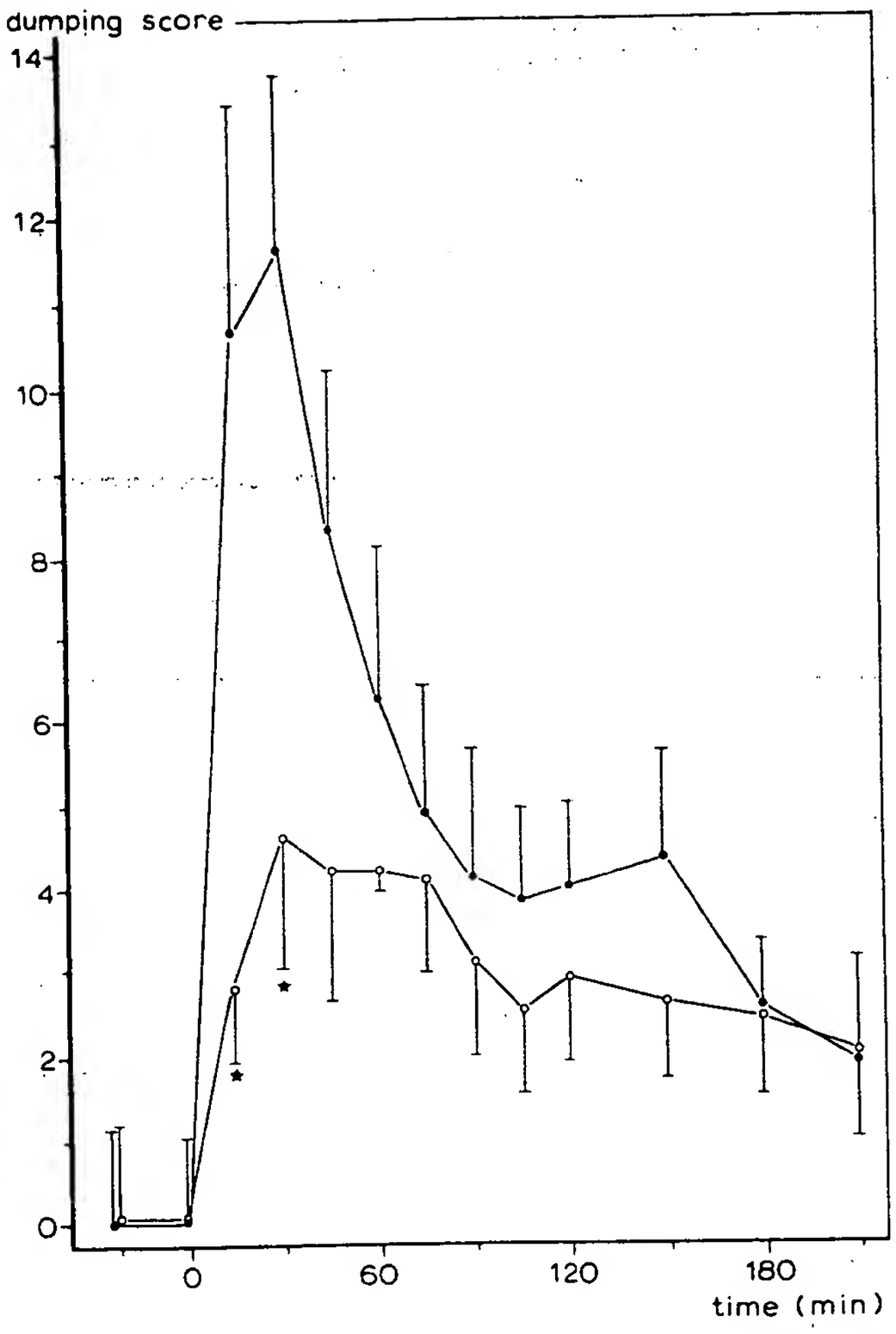

FIG. 1. Numerical dumping score after oral glucose with SMS 201-995 (○) and without SMS 201-995 (●) in six patients with early dumping. *Significant differences from placebo.

symptoms at least 60 minutes after the oral glucose load. Each patient was studied on two occasions after an overnight fast. In random order and in a double-blind fashion either 50 μg SMS 201-995 or placebo was administered subcutaneously 15 minutes before ingestion of 50 g glucose/m^2 body surface. Before ingestion of the 50% glucose solution in water and at regular intervals thereafter, patients were questioned about their symptoms and allocated a dumping score according to Sigstad.[13] Pulse rate was counted and blood samples were drawn at −25, −20, −15, 0, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 195, and 210 minutes. Before ingestion of the meal and at 30-minute intervals during the study, end-expiratory gas samples were obtained for measurement of breath hydrogen.[14] In the patients with early dumping the blood samples were used to measure packed cell volume. In patients with late dumping, these samples served to measure plasma glucose and plasma insulin levels.[15] Packed cell volume and plasma glucose were measured by standard techniques.

Results were expressed as the mean ± 1 SEM. Statistical analysis was performed by Student's t-test for paired results. Wilcoxon's test for paired data was used to analyse dumping score. All patients gave informed consent before entering the study. The study was approved by the local ethical committee.

Results

Early Dumpers

During placebo injection dumping score increased to a peak value of 11.7 ± 2.1 at 30 minutes after meal ingestion indicating severe dumping (Fig. 1). During SMS 201-995 all patients experienced a dramatic improvement of postprandial symptoms. At 15 and at 30 minutes, dumping score during SMS 201-995 was sig-

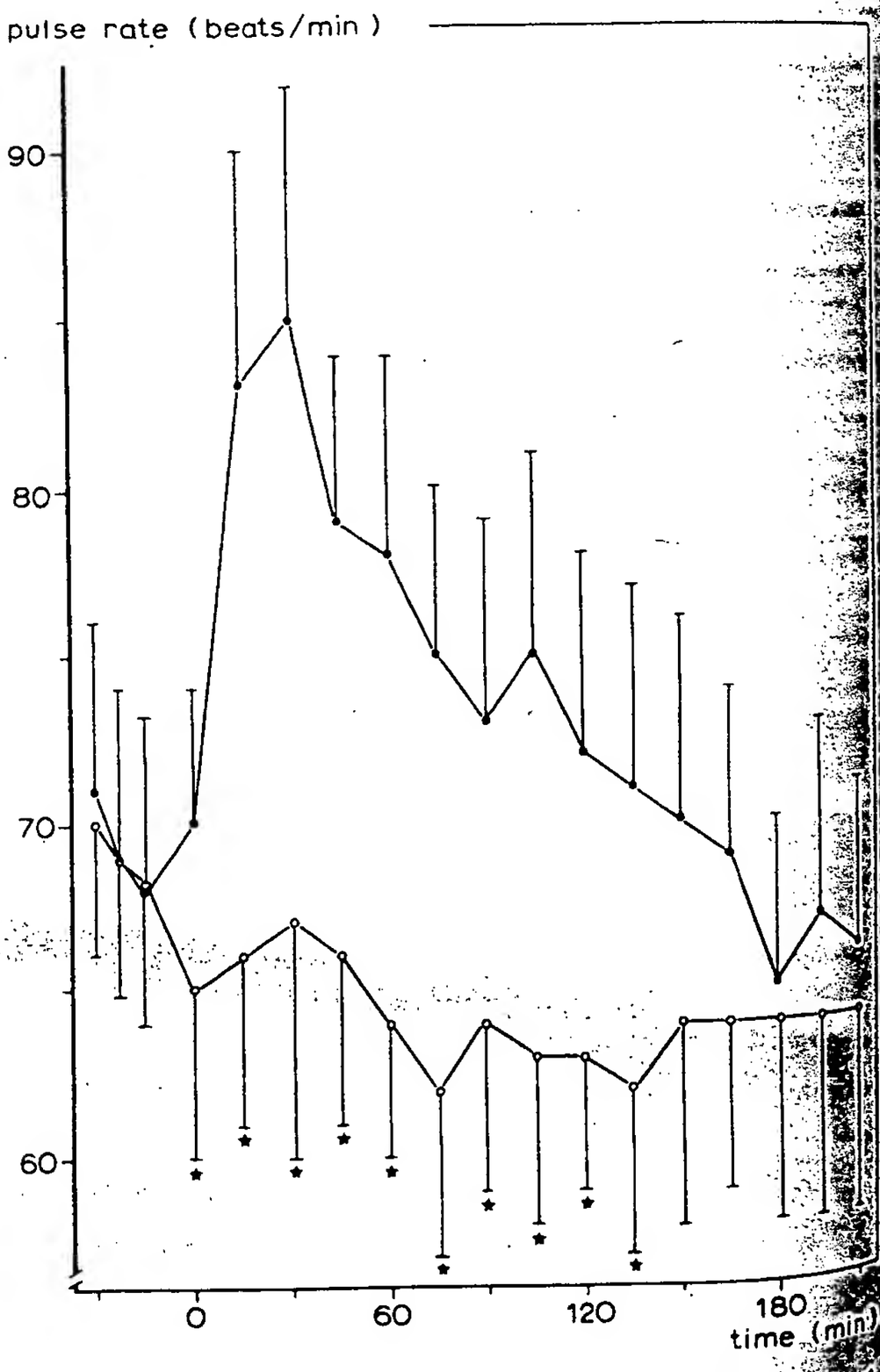

FIG. 2. Pulse rate after oral glucose with SMS 201-995 (○) and without SMS 201-995 (●) in six patients with early dumping. *Significant differences from placebo.

nificantly lower than that during placebo ($p < 0.05$; Fig. 1). Maximum dumping score during SMS 201-995 was 4.6 ± 1.6 at 30 minutes ($p < 0.05$ *vs.* placebo). Pulse rate increased from a basal value of 70 ± 4 beats/min to a maximum value of 85 ± 7 beats/min at 30 minutes after meal ingestion during placebo ($p < 0.05$, Fig. 2). On the other hand, SMS 201-995 abolished this postprandial rise in pulse rate (Fig. 2). Pulse rate during SMS 201-995 was significantly lower than that during placebo from 0 to 135 minutes ($p < 0.05$ to $p < 0.005$, Fig. 2).

Packed cell volume rose from 0.38 ± 0.02 L/L to 0.41 ± 0.02 L/L at 30 minutes during placebo ($p = 0.0005$, Fig. 3), and from 0.39 ± 0.02 L/L to 0.41 ± 0.02 L/L during SMS 201-995 ($p < 0.05$, Fig. 3). No significant differences were observed between packed cell volume during placebo and packed cell volume during SMS 201-995.

Four patients had a breath hydrogen excretion of more than 15 ppm during placebo at 30–60 minutes indicating spillover of glucose to the colon, but only one patient during SMS 201-995 at 150 minutes.

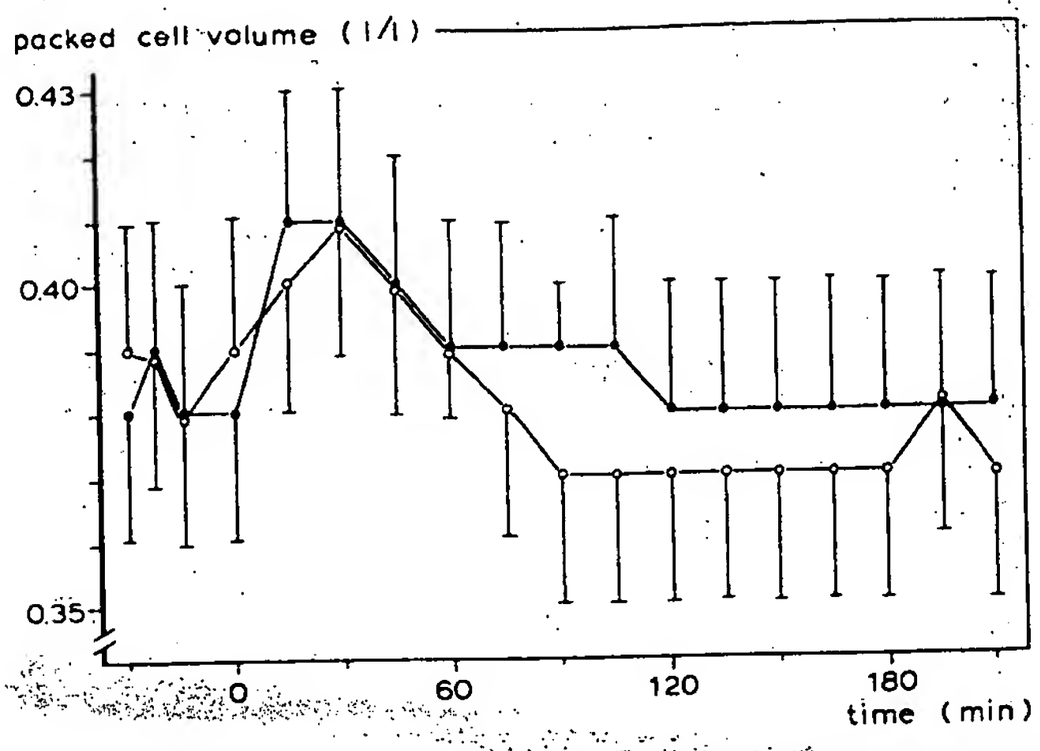

FIG. 3. Packed cell volume after oral glucose with SMS 201-995 (○) and without SMS 201-995 (●) in six patients with early dumping.

Late Dumpers

In patients suffering from reactive hypoglycemia, the initial rapid rise in plasma glucose was followed by a sharp decline to levels below 3.0 mmol/L from 105 to 135 minutes after the oral glucose load (Fig. 4). The reactive hypoglycemia observed during the placebo study was completely abolished by subcutaneous administration of SMS 201-995. From 60 to 210 minutes plasma glucose during SMS 201-995 was significantly higher than that during placebo ($p < 0.05$ to $p < 0.0005$, Fig. 4). Individual plasma glucose nadirs during placebo were 1.9 ± 0.3 mmol/L. During SMS 201-995 lowest individual plasma glucose levels were 7.5 ± 3.3 mmol/L ($p < 0.001$). SMS 201-995 attenuated plasma insulin response to glucose ingestion. Plasma insulin during SMS 201-995 was significantly lower than that during placebo at 30 and at 60 minutes ($p < 0.05$ to $p < 0.01$, Fig. 5). Peak plasma insulin level decreased from 173 ± 16 mU/L during placebo to 35 ± 9 mU/L during SMS 201-995 ($p < 0.05$). No patient experienced hypoglycemic symptoms during SMS 201-995. Three patients had a breath hydrogen excretion of more than 15 ppm during placebo at 15–60 minutes. On the other hand, during SMS 201-995 no patient presented with abnormal breath hydrogen excretion.

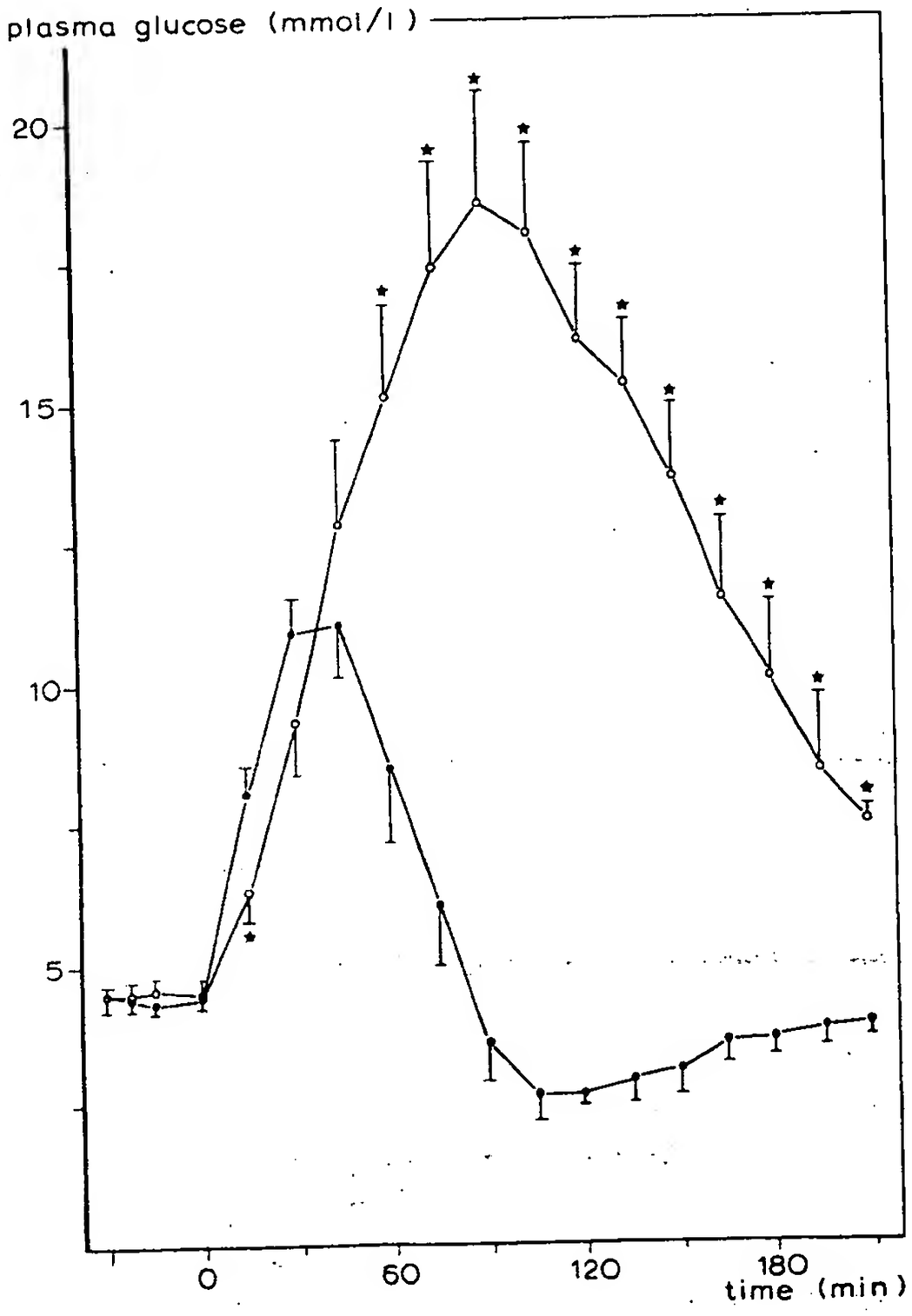

FIG. 4. Plasma glucose after oral glucose with SMS 201-995 (○) and without SMS 201-995 (●) in six patients with late dumping. *Significant differences from placebo.

Discussion

SMS 201-995 is a recently developed, long-acting analogue of somatostatin.[16] The circulating half-life of SMS 201-995 of about 100 minutes after subcutaneous injection is substantially longer than that of native somato-

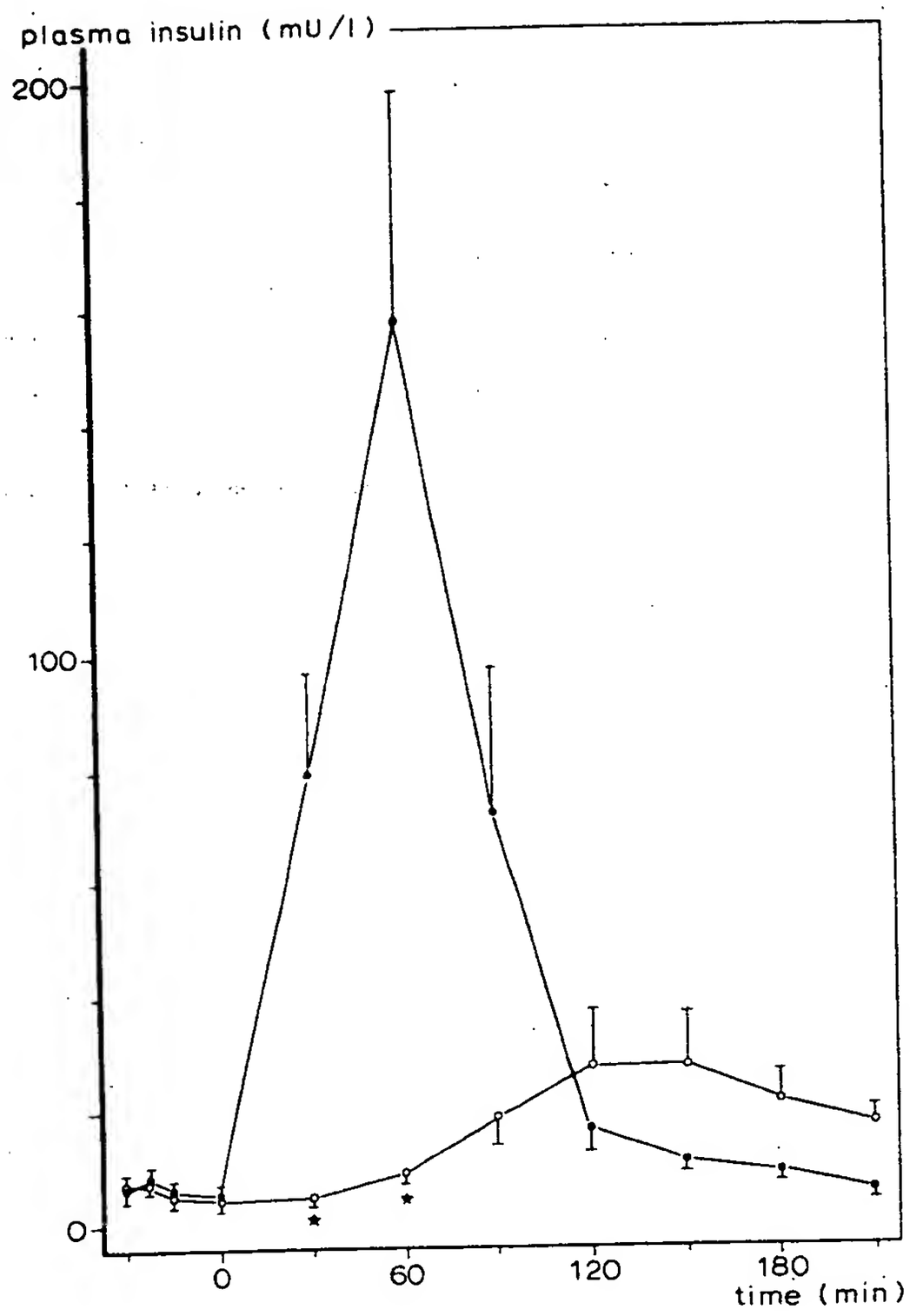

FIG. 5. Plasma insulin after oral glucose with SMS 201-995 (○) and without SMS 201-995 (●) in six patients with late dumping. *Significant differences from placebo.

statin, which is only 2 to 3 minutes.[16] SMS 201-995 inhibits release of growth hormone, and it has been used successfully in the treatment of patients with acromegaly.[17] Similar to native somatostatin, SMS 201-995 inhibits release of several gastrointestinal peptides including insulin, glucagon, gastrin, gastric inhibitory polypeptide, pancreatic polypeptide, vasoactive intestinal polypeptide, and neurotensin.[18] SMS 201-995 was found to have a beneficial effect in the management of patients with insulinoma, glucagonoma, VIPoma, and carcinoid syndrome.[19,20]

The present study shows a dramatic improvement of postprandial dumping symptoms after subcutaneous injection of SMS 201-995 prior to meal ingestion in patients with previous gastric surgery. All patients with early dumping participating in the study suffered from severe postprandial complaints that had resisted other therapeutic efforts including addition of pectin or acarbose, an α-glucosidase inhibitor, to the meal. In these patients dumping score decreased from 12 to 5. McLoughlin et al.[9] treated patients with less severe dumping symptoms with acarbose. In these patients an improvement of the dumping score from only 6 to 4 was reported. Furthermore, during SMS 201-995, postprandial rise of pulse rate, a symptom associated with the dumping syndrome, was completely abolished. This action agrees with that of native somatostatin in dumping patients.[12]

The mechanism by which SMS 201-995 exerts its beneficial effect on postprandial dumping is not known. Somatostatin slows gastrointestinal transit.[21] Since rapid gastric emptying of food is generally considered to be of major importance in precipitating the dumping syndrome, the effect of SMS 201-995 might be mediated by slowing of gastrointestinal transit. Indeed, it was shown in the present study that abnormal breath hydrogen excretion indicating spillover of glucose to the colon, resulting from the rapid transit, became normal in three out of four patients with early dumping. An increase in postprandial splanchnic blood flow, together with a paradoxical increase of subcutaneous blood flow (plus a decrease in circulatory blood volume) has been suggested to be involved in the development of cardiovascular symptoms.[1,2,6] Because postprandial increase of packed cell volume was not significantly affected by SMS 201-995, it is unlikely that SMS 201-995 exerted its beneficial effect by preventing plasma volume depletion. On the other hand, the beneficial effect of SMS 201-995 on circulatory disturbances might be related to a direct pressor effect on splanchnic hemodynamics. Indeed, it was recently reported that SMS 201-995 inhibited splanchnic blood flow similar to native somatostatin.[22,23] Furthermore, a pressor effect of SMS 201-995 was demonstrated in patients suffering from postprandial hypotension.[24] Another possibility is that SMS 201-995 similar to native somatostatin inhibited excessive release of vasoactive substances from the gut that have been increminated in the pathogenesis of circulatory disturbances.[1,2,4,5,7,12] It is interesting to note that SMS 201-995 also improved circulatory symptoms in patients with the carcinoid syndrome.[20]

In patients suffering from late dumping, SMS 201-995 was highly effective for the prevention of reactive hypoglycemia. Even after administration of a powerful challenge of carbohydrate metabolism by a concentrated glucose meal, during SMS 201-995 the lowest plasma glucose level was well above hypoglycemic values. No complaints of hypoglycemia were reported during SMS 201-995. The beneficial effect of SMS 201-995 is probably related to inhibition of excessive insulin release in the early postprandial phase as demonstrated in the present study. Furthermore, inhibition of intestinal hurry as reflected by breath hydrogen excretion allowing

glucose to be present in the small intestine for absorption in the late postprandial phase, probably contributes to the beneficial effect of SMS 201-995. α-Glucosidase inhibitors have been recommended in patients suffering from postprandial reactive hypoglycemia.[9–11] However, these substances induced serious side effects due to malabsorption of carbohydrates.[10,11] In contrast, SMS 201-995 subsided malabsorption of carbohydrates in all patients with late dumping.

Long-term studies have demonstrated good tolerance of SMS 201-995 in the treatment of patients with acromegaly, carcinoid syndrome, and other endocrine tumors of the gut.[17,19,20,24,25] In these patients no serious side effects were reported. Similarly, in the present study SMS 201-995 was well tolerated by all patients without any side effects.

We conclude that SMS 201-995 is highly effective for the prevention of symptoms and signs related to the dumping syndrome. It reduces tachycardia and peak plasma insulin level, and it prevents reactive hypoglycemia with spillover of glucose to the colon. Since SMS 201-995 is well tolerated, it holds promise as a powerful therapeutic agent in patients with disabling postprandial dumping after previous gastric surgery.

Acknowledgments

The authors are indebted to Professor T. J. Benraad, Ph.D., and to J. C. M. Hafkenscheid, Ph.D., and to H. W. Verbruggen for laboratory measurements. SMS 201-995 was kindly supplied by SANDOZ, Uden, The Netherlands.

References

1. Fromm D. Complications of gastric surgery. *In* Dietschy JM, ed. Clinical Gastroenterology Monograph Series. London: John Wiley and Sons, 1977; 7–34.
2. Woodward ER. The early postprandial dumping syndrome: clinical manifestations and pathogenesis. *In* Bushkin FL, Woodward ER. eds. Postgastrectomy Syndromes. Philadelphia: WB Saunders, 1976; 28–33.
3. Woodward ER, Neustein CL. The late postprandial dumping syndrome. *In* Bushkin FL, Woodward ER, eds. Postgastrectomy Syndromes. Philadelphia: WB Saunders, 1976; 28–33.
4. Blackburn AM, Christofides ND, Ghatei MA, et al. Elevation of plasma neurotensin in the dumping syndrome. Clin Sci 1980; 59:237–243.
5. Sagor GR, Bryant MG, Ghatei MA, et al. Release of vasoactive intestinal peptide in the dumping syndrome. Br Med J 1981; 282:507–510.
6. Lawaetz O, Aritas Y, Blackburn AM, Ralphs DNL. Gastric emptying after peptic ulcer surgery. Scand J Gastroenterol 1982; 17:1065–1072.
7. Lawaetz O, Blackburn AM, Bloom SR, et al. Gut hormone profile and gastric emptying in the dumping syndrome: Scand J Gastroenterol 1983; 18:73–80.
8. Jenkins DJA, Gassull MA, Leeds AR, et al. Effect of dietary fiber on complications of gastric surgery: prevention of postprandial hypoglycemia by pectin. Gastroenterology 1977; 72:215–217.
9. McLoughlin JC, Buchanan KD, Alam MJ. A glycoside-hydrolase inhibitor in treatment of dumping syndrome. Lancet 1979; 2:603–605.
10. Speth PAJ, Jansen JBMJ, Lamers CBHW. Effect of acarbose, pectin, and placebo on postprandial reactive hypoglycaemia after gastric surgery. Gut 1983; 24:798–802.
11. Lyons TJ, McLoughlin JC, Shaw C, Buchanan KD. Effect of acarbose on biochemical responses and clinical symptoms in dumping syndrome. Digestion 1985; 31:89–96.
12. Long RG, Adrian TE, Bloom SR. Somatostatin and the dumping syndrome. Br Med J 1985; 290:886–888.
13. Sigstad H. A clinical diagnostic index in the diagnosis of the dumping syndrome. Acta Med Scand 1970; 188:479–486.
14. Metz G, Gassull MA, Leeds AR, et al. A simple method of measuring breath hydrogen in carbohydrate malabsorption by end-expiratory sampling. Clin Sci 1976; 50:237–240.
15. Yalow RS, Berson SA. Immunoassay of endogenous plasma insulin in man. J Clin Invest 1960; 39:1157–1175.
16. Bauer W, Briner U, Doepfner W, et al. SMS 201-995: a very potent and selective octapeptide analogue of somatostatin with prolonged action. Life Sci 1982; 31:1133–1140.
17. Lamberts SWJ, Uitterlinden P, Verschoor L, et al. Long-term treatment of acromegaly with the somatostatin analogue SMS 201-995. N Engl J Med 1985; 313:1576–1580.
18. Williams G, Fuessl H, Kraenzlin M, Bloom SR. Postprandial effects of SMS 201-995 on gut hormones and glucose tolerance. Scand J Gastroenterol 1986; 21(suppl 119):73–83.
19. Anderson JV, Bloom SR. Neuroendocrine tumours of the gut: long-term therapy with the somatostatin analogue SMS 201-995. Scand J Gastroenterol 1986; 21(suppl 119):115–128.
20. Kvols LK, Moertel CG, O'Connel MJ, et al. Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. N Engl J Med 1986; 315:663–666.
21. Johansson C, Wisén O, Efendic S, Uvnäs-Wallensten K. Effects of somatostatin on gastrointestinal propagation and absorption of oral glucose in man. Digestion 1981; 22:126–137.
22. Wahren J, Eriksson LS. The influence of a long-acting somatostatin analogue on splanchnic haemodynamics and metabolism in healthy subjects and patients with liver cirrhosis. Scand J Gastroenterol 1986; 21(suppl 119):103–108.
23. Wahren J, Felig P. Influence of somatostatin on carbohydrate disposal and absorption in diabetes mellitus. Lancet 1976; 2:1213–1216.
24. Hoeldtke RD, O'Dorisio TM, Boden G. Treatment of autonomic neuropathy with a somatostatin analogue SMS 201-995. Lancet 1986; 2:602–605.
25. Verschoor L, Lamberts SWJ, Uitterlinden P, Del Pozo E. Glucose tolerance during long term treatment with a somatostatin analogue. Br Med J 1986; 293:1327–1328.